An update on the pathogenesis and treatment of IgA nephropathy

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Over the past two decades significant progress has been made in unravelling the complex pathogenesis of immunoglobulin A nephropathy (IgAN). Excess amounts of poorly galactosylated immunoglobulin (Ig)A1 in the serum appear to be the trigger for generation of glycan-specific IgG and IgA autoantibodies, resulting in the formation of circulating IgA immune complexes, which are pivotal to the development of nephritis. It remains unclear why there is an increase in poorly galactosylated IgA1 molecules in the serum in IgAN. One intriguing possibility is that this IgA is derived from displaced mucosal B cells, which have mis-homed from their mucosal induction sites to systemic sites, where they secrete polymeric, poorly galactosylated IgA directly into the circulation rather than onto mucosal surfaces. Lack of a clear appreciation of the origins of poorly galactosylated IgA1 and an incomplete understanding of immune complex formation have hampered development of specific therapeutic strategies to prevent mesangial IgA deposition. Clinicians have therefore been left to manage patients with generic therapies, mainly by control of blood pressure and renin–angiotensin blockade. A paucity of high-quality clinical trials has meant that evaluation of additional therapies, particularly immunosuppressive regimens, has been difficult and there remains a great deal of confusion over the optimum treatment of patients at high risk of progressive chronic kidney disease.

Kidney International (2012) **81,** 833–843; doi:10.1038/ki.2011.501; published online 8 February 2012

KEYWORDS: IgA; IgA deposition; IgA nephropathy; immune complexes

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Received 2 August 2011; revised 6 October 2011; accepted 11 October 2011; published online 8 February 2012

The year 2011 marked the death of Jean Berger, the Parisian pathologist who published the first description of immunoglobulin A nephropathy (IgAN) in 1968.[1] Since this first description some 43 years ago, great strides have been made in understanding the pathogenesis of this common glomerulonephritis (GN), and we review these key abnormalities in the first part of this review. Unfortunately, this increase in our understanding has yet to translate into specific therapies capable of disrupting IgA immune complex formation or glomerular IgA deposition. The treatment strategies we discuss in the second part of this review will, therefore, be very familiar to all nephrologists, as they are those commonly employed in nearly every form of glomerular disease.

PATHOGENESIS OF IgA NEPHROPATHY

The single diagnostic feature of IgAN is the finding of immune deposits predominantly containing polymeric IgA in the glomerular mesangium on renal biopsy. An explanation for this finding, and the clinical sequelae with which it is associated, has been the subject of considerable investigation. Despite advances in our understanding of the IgA immune system in health and the identification of a number of key changes in IgA biology in IgAN, no one unifying pathological mechanism has been found to explain the development of IgAN. In particular, there is a striking disparity between presentation, clinical course, and pathological findings—the extent of IgA deposition does not correlate with the degree of renal injury or clinical history—raising the likelihood that it is the interaction between two or more susceptibility factors that influences the outcome. Indeed, such is the diversity of clinical presentation and disparity with histological and basic laboratory findings that there may be several distinct pathological mechanisms capable of leading to the common histological end point of mesangial IgA deposition and glomerular injury, implying IgAN may describe a number of distinct disease entities.

IgA1 *O*-glycosylation

It has been over 15 years since an excess of poorly galactosylated IgA1 was found to be present both in the serum and in the glomerular immune deposits of patients with IgAN.[2,3] This key observation has subsequently been

consistently reproduced in populations from North America, Europe, and Australasia and considerable work has been undertaken to establish the cause and pathological consequence of alterations in the complement of serum IgA1 *O*-glycoforms in IgAN.[3–6]

IgA1 contains a 17-amino-acid hinge region, which undergoes co/post translational modification by the addition of up to six *O*-glycan chains (Figure 1).[7] These chains comprise *N*-acetylgalactosamine (GalNAc) in *O*-linkage with either serine or threonine residues. Galactose may be β1, 3-linked to GalNAc by the enzyme C1GalT1 (core 1 β1,3 galactosyltransferase), which requires a molecular chaperone, Cosmc (core 1 β1,3 galactosyltransferase molecular chaperone), to ensure its correct folding and stability. Both the galactose residue and GalNAc may be sialylated in the α2,3- or α2,6-configuration, respectively. It has been proposed that addition of sialic acid (*N*-acetylneuraminic acid, NeuNAc) to GalNAc prevents the further addition of galactose, and so activity of the enzyme α2,6 sialyltransferase may be critical to the generation of poorly galactosylated IgA1 *O*-glycoforms.[8] Several groups have examined glycosyltransferase expression and function in IgAN; however, results have been inconclusive, with some suggesting downregulation of C1GalT1 and/or Cosmc is the key event,[9–11] while others report the driving factor in production of poorly galactosylated IgA1 in IgAN is excessive sialylation of GalNAc by α2,6 sialyltransferase.[8] Indeed, it may well be a combination of these two patterns that results in changes in IgA1 *O*-glycosylation.

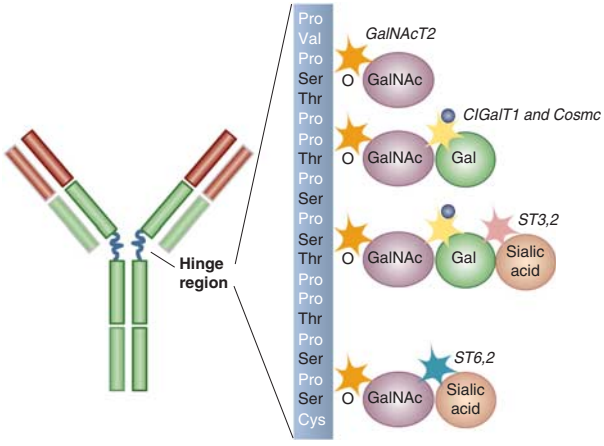

Figure 1 | *O*-glycosylation of immunoglobulin (Ig)A1. IgA1 *O*-glycosylation results from the stepwise addition of monosaccharides to serine or threonine residues in the IgA1 hinge region. There are nine possible sites for *O*-glycosylation in each α heavy chain, although only six may be occupied at any time. To begin with, *N*-acetylgalactosamine (GalNAc) is *O*-linked to either serine or threonine residues by the activity of *N*-acetylgalactosaminyltransferase (GalNAcT2). Galactose (Gal) may be β1,3-linked to GalNAc; this requires the action of core 1 β1,3 galactosyltransferase (C1GalT1) and its molecular chaperone core 1 β1,3 galactosyltransferase molecular chaperone (Cosmc), which ensures its correct folding and stability. Galactose may or may not be sialylated by α2,3 sialyltransferase (ST3,2). In addition, sialic acid (*N*-acetylneuraminic acid, NeuNAc) may be attached directly to GalNAc in an α2,6 linkage under the control of α2,6 sialyltransferase (ST6,2). Sialylation of GalNAc is thought to prevent the future addition of galactose. Cys, cysteine; Pro, proline; Ser, serine; Thr, threonine.

It has been recognized for some time that in a single individual there is a spectrum of IgA1 *O*-glycoforms that collectively contribute to the overall measured IgA1 *O*-glycosylation of an individual serum sample.[3,6,7] This suggests that IgA1 *O*-glycosylation is differentially regulated in IgA1-secreting plasma cells. The factors that control IgA1 *O*-glycosylation are, currently, not known. It is clear, however, that in health *O*-glycosylation varies depending on the site of IgA1 production, and this is likely in part related to the local cytokine milieu.[11–13] IgA1 synthesized from mucosally primed B cells is relatively poorly galactosylated compared with IgA1 synthesized from systemically primed B cells.[13] There is also evidence that *O*-glycosylation is differentially regulated during B-cell maturation and class switching after antigen encounter.[14] In healthy subjects, IgD is galactosylated more heavily but less sialylated than IgA1, suggesting galactosylation is normally downregulated in IgA1-secreting cells and sialyltransferases are upregulated after class switching. The pattern of IgD *O*-glycosylation is normal in patients with IgAN, implying that the changes in IgA1 *O*-glycosylation patterns in IgAN are not shared by IgD, and are therefore not caused by defective expression or function of glycosylating enzymes affecting the entire B-cell lineage.

There is also now convincing evidence from US and Chinese familial and sporadic IgAN cohorts that genetic factors heavily influence the composition of circulating IgA1 *O*-glycoforms in serum.[15–17] The presence of high levels of poorly galactosylated IgA1 in unaffected relatives of patients with both familial and sporadic IgAN suggests that additional factors are required for changes in IgA1 *O*-glycosylation to translate into clinical disease.

Immune complex formation

IgAN is increasingly considered an immune complex deposition disease.[18] Deposited immune complexes always contain IgA1 as either the dominant or the co-dominant antibody, but also frequently contain other antibody classes. It is speculated that changes in the complement of IgA1 hinge region sugars result in a conformational change of the IgA1 molecule exposing novel epitopes within the hinge region, which are recognized as neoantigenic targets. A number of investigators have identified autoreactive IgG and IgA1 antibodies with specificity for the IgA1 hinge region in the serum in IgAN.[19–21] The trigger for autoantibody and subsequently immune complex formation in IgAN is not known; however, two recently published genome-wide association studies in sporadic IgA reported that the human leukocyte antigen region contains susceptibility alleles predisposing to IgAN.[22,23] This association with human leukocyte antigen is at least compatible with susceptible patients preferentially presenting specific self-antigens that promote the generation

of glycan-specific antibodies. Furthermore, it has been shown that IgAN is associated with a specific switch from proteasome to immunoproteosome expression in peripheral blood mononuclear cells.[24] This phenotypic switch to a more catalytic proteasome suggests an increased efficiency of antigen processing and presentation in IgAN. The trigger for this switch in proteasome has been postulated to be a host response to immune challenges, possibly from viral infections that trigger interferon-γ release.

An alternative, or perhaps complementary, hypothesis is that hinge region reactive autoantibodies are microbial-specific mucosal antibodies generated against carbohydrates present in microbial cell walls. By chance these microbial-specific antibodies cross-react with the poorly galactosylated IgA1 hinge region, and therefore during periods of mucosal infection immune complex formation is promoted by increasing levels of autoantibody, which may be further accentuated by pathogen-induced switching to the immunoproteosome and enhanced microbial antigen presentation. What is more, microbial-specific IgA1 generated at mucosal surfaces may in itself contribute to the pool of self-antigen, as mucosal IgA1 is relatively poorly galactosylated. The possibility of molecular mimicry having a part in immune complex formation may help explain the well-recognized association of visible hematuria with episodes of mucosal infection in IgAN.

Another potential contributory factor to immune complex formation in IgAN is the myeloid Fc receptor for IgA, CD89. CD89 is present on myeloid cells and exists in membrane-bound and soluble forms (sCD89). Three isoforms of sCD89 have been described *in vitro*, although only two of these have been found *in vivo*.[25–27] Both *in vivo* isoforms are postulated to have a role in immune complex formation in IgAN. The larger sCD89 isoform (50–70 kDa) has been identified only in the serum of patients with IgAN. It is proposed that in IgAN binding of polymeric IgA to membrane-bound CD89 causes shedding of this larger isoform, which results in formation of circulating complexes that are prone to mesangial deposition.[25] By contrast, the smaller 30-kDa soluble isoform is present in the serum of both patients and healthy subjects, and high levels of IgA complexed to this smaller isoform levels have been shown to be protective against development of progressive renal disease.[26,27] Despite these interesting observations, and the potential for sCD89 to act in both a pathogenic and a protective way in IgAN, it is difficult to gauge the importance of sCD89 in immune complex formation as there is to date no convincing evidence that CD89 is present in mesangial IgA deposits.

The origins of pathogenic IgA in IgA nephropathy

Accepting that immune complex formation is pivotal to IgA deposition and triggering of glomerular injury, and that the substrate for immune complex formation in IgAN appears to be an excess of poorly galactosylated IgA1 *O*-glycoforms, where does this IgA1 come from? IgA1 is secreted by antibody-secreting B cells in distinct mucosal and systemic compartments[28] with a characteristic site-specific phenotype.[13,29] In particular, mucosal IgA is typically polymeric and of low affinity, while systemic IgA is predominantly of high affinity and monomeric. Furthermore, IgA1 specific for mucosally encountered antigens is relatively poorly galactosylated. All these properties of mucosal IgA1 are characteristic of serum and mesangial IgA1 in IgAN.[2,30,31] What is more, the classical clinical picture in IgAN of recurrent episodes of visible hematuria coinciding with mucosal infection again points to the mucosal IgA immune system as the source of poorly galactosylated IgA1 *O*-glycoforms. However, the numbers of polymeric IgA-secreting plasma cells are reduced at mucosal sites in IgAN,[32] while their numbers are increased in systemic sites, in particular the bone marrow.[33] To explain the mucosal phenotype of mesangial IgA in the context of reduced mucosal IgA plasma cells, it has been proposed that, following normal mucosal priming, a proportion of antigen-committed IgA plasmablasts mis-traffic to systemic sites instead of homing back to the mucosal site of antigen encounter (Figure 2). This mis-trafficking may occur because of faulty expression of surface homing receptors on lymphocyte subsets or defective expression of mucosal chemokines and homing counter-receptors on mucosal vascular endothelium.[28,34–36] These translocated cells take up residence in the bone marrow, and perhaps tonsils, where they secrete 'normal' mucosal-type IgA into the systemic circulation. Over time there is a gradual accumulation of mucosally derived IgA plasma cells in systemic sites; levels of poorly galactosylated IgA1 *O*-glycoforms increase and plateau, forming a circulating pool of molecules, which, in susceptible individuals, provide the antigenic stimulus for autoantibody formation and immune complex generation.

If displaced mucosal plasma cells are the source of the poorly galactosylated IgA1 *O*-glycoforms, understanding how they regulate IgA synthesis and control IgA1 *O*-glycosylation will be essential if effective treatments are to be developed. One particular area of interest currently is the role of Toll-like receptors (TLRs) in driving IgA synthesis and perhaps even modifying glycosyltransferase activity. TLRs have key functions in innate immunity to microbial pathogens via recognition of a diverse range of pathogen-associated molecular patterns, such as bacterial lipopolysaccharide, RNAs, and DNAs.[37] B cells express a number of TLRs, but those most likely to have a role in IgAN are TLR4, TLR9, and TLR10.[38–40] Most importantly, ligation of TLR9 leads to polyclonal activation of B cells, class switching, and Ig production. IgA secretion by mucosal lamina propria B cells is increased after TLR9 stimulation, implying that mucosal B cells can recognize pathogen-associated molecular patterns and secrete IgA in a T-cell–independent manner.[41] What is more, ligation of B-cell TLR4 by bacterial lipopolysaccharide induces methylation of the Cosmc gene, leading to reduced activity of C1GalT1 and undergalactosylation of IgA1.[40] Whether B-cell TLR expression is increased in IgAN is not known; however, these early data suggest that mucosal

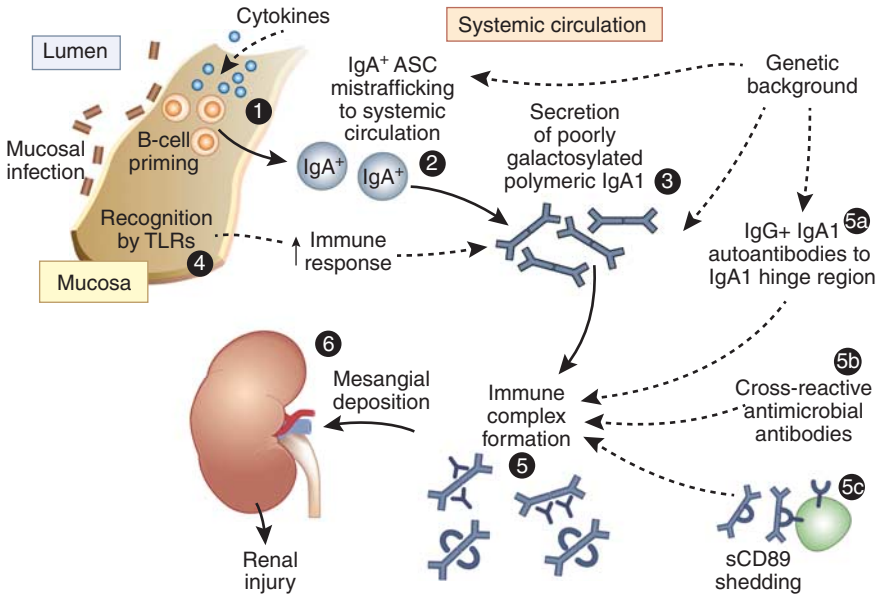

Figure 2 | An overview of the pathogenesis of immunoglobulin (Ig)A nephropathy. (1) Mucosal infection primes naive B cells to class switch to become IgA$^+$ antibody-secreting cells (ASCs) through both T-cell–dependent (cytokine mediated) and T-cell–independent (Toll-like receptor (TLR) ligation) pathways. (2) Some IgA$^+$ ASC mis-home to the systemic compartment during lymphocyte trafficking. (3) Displaced IgA$^+$ ASCs take up residence in systemic sites and secrete normal 'mucosal-type' (poorly galactosylated and polymeric) IgA1 into the systemic circulation. (4) IgA1 secretion by displaced mucosal ASC is augmented by TLR ligation from mucosal-derived pathogen-associated molecular patterns, which have entered the systemic compartment. (5) IgA1 immune complexes form in the systemic circulation. Poorly galactosylated polymeric IgA1 molecules are the substrate for immune complex formation and combine with: (a) IgG and IgA autoantibodies reactive to exposed neoepitopes in the poorly galactosylated IgA1 hinge region; (b) antimicrobial antibodies specific for carbohydrate components of the microbial cell wall, which are cross-reactive with the poorly galactosylated IgA1 hinge region; (c) soluble CD89 that is shed from myeloid cells in response to polymeric IgA1 binding. (6) IgA1 immune complexes deposit in the mesangium through a combination of mesangial trapping and increased affinity of poorly galactosylated IgA1 for extracellular matrix components. Immune complex deposition triggers a series of downstream pathways leading to glomerular injury and tubulointerstitial scarring.

pathogens may not only be able to influence immune complex formation through generation of cross-reactive antibodies, but also specifically stimulate IgA synthesis and modulate glycosylation of the IgA antibody.

Upregulation of TLR4 has been reported on circulating monocytes in IgAN and in particular in patients with proteinuria and visible hematuria, suggesting monocytic TLR4 engagement may provide a link between mucosal infection and the development of glomerular inflammation in IgAN.[42]

Mesangial IgA deposition, glomerular injury, and tubulointerstitial damage

IgA immune complex deposition occurs through a combination of mesangial trapping and increased affinity of poorly galactosylated IgA1 *O*-glycoforms to extracellular matrix components including fibronectin and type IV collagen.[43,44] A key area of interest over the past 10 years has been elucidating the effect of IgA deposition on mesangial cell, podocyte, and proximal tubular cell function (Figure 3). The recently published Oxford Classification of IgAN identified four key pathologic consequences of IgA deposition that independently determine the risk of developing progressive renal disease: mesangial cell proliferation (M), endocapillary proliferation (E), segmental glomerulosclerosis (S), and tubulointerstitial scarring (T).[45] There is increasing evidence, predominantly from *in vitro* models, that IgA immune complexes containing poorly galactosylated IgA1 *O*-glycoforms bind to and activate mesangial cells, the pivotal event in driving glomerular injury in IgAN. Recognition of deposited IgA immune complexes is mediated by an ill-defined group of mesangial IgA receptors, one of which is the transferrin receptor (CD71). Binding results in proliferation (M) and release of proinflammatory and profibrotic mediators.[46–48] These mediators, along with the direct effects of exposure to IgA immune complexes, cause podocyte injury, a process fundamental to segmental glomerular scarring (S)[49–51] and proximal tubular epithelial cell (PTEC) activation, which drives tubulointerstitial scarring (T).[52]

With increasing damage to the permselective barrier, increasing amounts of high-molecular-weight IgA immune complexes enter the urine. In IgAN, these immune complexes are enriched for poorly galactosylated IgA1 *O*-glycoforms, presumably reflecting their predisposition for trapping within the mesangium.[53] It is therefore likely that podocytes and PTEC are constantly exposed to filtered IgA immune complexes once the glomerular size barrier is impaired. Much effort has focused on understanding the interaction of poorly galactosylated IgA1 *O*-glycoforms with mesangial cells and the effect of mesangial-derived inflammatory mediators on

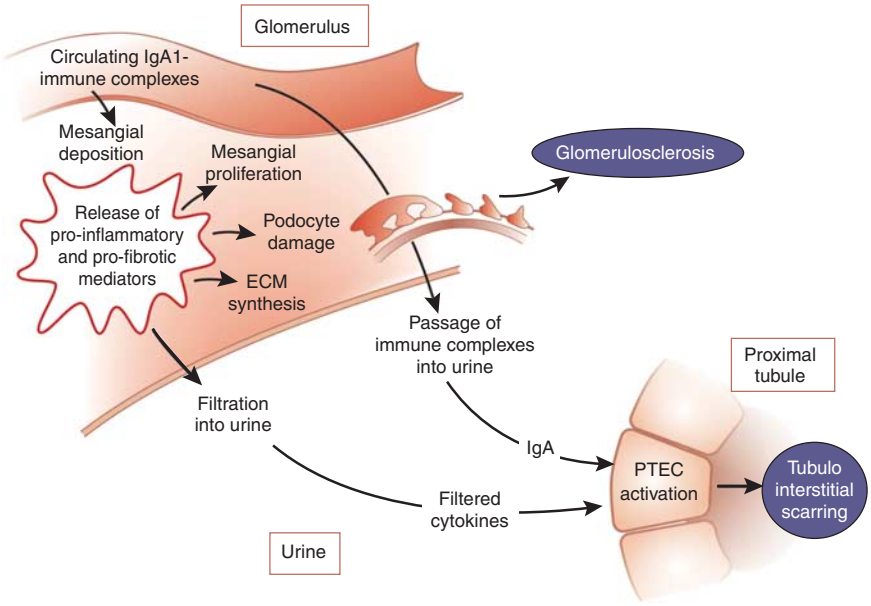

Figure 3 | Immunoglobulin (Ig)A immune complex deposition and triggering of glomerular and tubulointerstitial injury. Mesangial IgA1 immune complexes bind to the transferrin receptor (CD71) on mesangial cells and trigger mesangial cell activation, resulting in release of pro-inflammatory and pro-fibrotic mediators and mesangial cell proliferation. Released soluble mediators act in locally enhancing mesangial proliferation, extracellular matrix (ECM) synthesis, and podocyte damage (glomerulopodocytic crosstalk). Mesangial cell-derived mediators are also filtered into the urine, where they activate proximal tubular epithelial cells (PTECs) and thereby promote tubulointerstitial scarring (glomerulotubular crosstalk). Glomerular injury and increasing damage to the permselective barrier permit passage of large immune complexes across the glomerular basement membrane, where they come into direct contact with podocytes and PTEC. Little is known of the effects of IgA-containing immune complexes on podocytes and PTEC, although data suggest both cell types are able to bind IgA. If left unchecked, continued immune complex deposition and mesangial cell activation lead to progressive glomerulosclerosis through excessive ECM deposition and irreversible podocyte loss. Increasing non-selective proteinuria exposes PTEC to albumin, mesangial-derived mediators, and IgA immune complexes, the combination of which results in a pro-inflammatory and pro-fibrotic transformation of PTEC and relentless tubulointerstitial scarring, the harbinger of end-stage renal disease.

podocyte and PTEC function. However, little is known about the interaction of IgA immune complexes with podocytes and PTEC despite the fact that both cell types can bind IgA, albeit with lower affinity than mesangial cells.[49,52] It is tempting to speculate that distinct properties of IgA immune complexes might promote IgA deposition, but others separately drive mesangial activation (M, mesangial hypercellularity), podocyte injury (S, segmental glomerulosclerosis), and PTEC transformation (T, tubular atrophy/interstitial fibrosis). If this is the case and we can identify these properties, it will ultimately resolve the clear disparity seen in clinical practice between the ubiquitous presence of mesangial IgA and the wide spectrum of clinical outcomes in IgAN.

The genetics of IgA nephropathy

There is now clear evidence across several ethnic backgrounds that the composition of serum IgA1 *O*-glycoforms is a heritable trait.[15–17] However, the genetic basis for this observation remains unknown. Separate linkage studies in familial cases of IgAN and genome-wide association studies in both sporadic and familial IgAN suggest that there is a genetic component to IgAN.[22,23,54–56] Several susceptibility loci have been identified, although, interestingly, none of these encode genes involved in *O*-glycosylation. Two recent genome-wide association studies, one in UK patients and the other in a Chinese Han population, identified loci on chromosome 6p within the region coding for the major histocompatibility complex.[22,23] Mutations in major histocompatibility complex genes have been associated with several autoimmune conditions, and, as already alluded to, these observations would be consistent with the predisposition to develop IgA1 hinge region autoantibodies, at least in some cases. Not surprisingly, a number of studies have screened the genes coding for the IgA1 *O*-glycosyltransferases using single-nucleotide polymorphisms, but results have been inconsistent and no firm conclusions can be drawn.

What is clear from the available evidence is that patients with IgAN can produce highly galactosylated IgA1 (and IgD) and that changes in IgA1 *O*-glycosylation do not necessarily have to involve mutations in glycosyltransferase genes. We have discussed a number of external factors that modulate IgA synthesis and glycosyltransferase expression, including cytokines within the local microenvironment, TLR, and B-cell programming at the time of antigen encounter. Future studies may, therefore, wish to focus on defining glycosyltransferase expression in specific B-cell subsets, particularly mucosally primed B cells, and elucidating the influence of factors outside of the immediate glycosylation pathway on IgA1 *O*-glycosylation in order to identify plausible candidate genes.

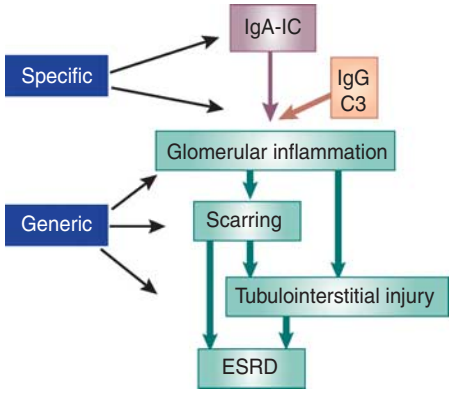

Figure 4 | Approaches to treatment in immunoglobulin (Ig)A nephropathy. Owing to the lack of specific therapies capable of preventing IgA immune complex (IgA-IC) formation and mesangial IgA deposition, current therapeutic strategies mainly target the damaging downstream consequences of IgA deposition, and are limited to treatments generic to other glomerular diseases. ESRD, end-stage renal disease.

TREATMENT STRATEGIES IN IgA NEPHROPATHY

Despite progressive advances in our understanding of the pathogenesis of IgAN, there is still no available treatment to alter the production of pathogenic IgA immune complexes or prevent their mesangial deposition. Treatment options therefore center on modulating downstream immune and inflammatory events in the glomerulus and tubulointerstitium. Many of the current treatment strategies are therefore generic to other forms of chronic glomerular diseases, that is, renin–angiotensin blockade, reduction of proteinuria, and blood pressure (BP) control (Figure 4).

Challenges facing evaluation of drug therapy in IgA nephropathy

Although an increasing number of randomized controlled trials (RCTs) of therapies for IgAN are being published, there are a number of issues that must be considered when planning and interpreting clinical trials in IgAN. First, it is not clear that all patients with mesangial IgA deposition share a common disease process. Also, response to IgA deposition may vary between individuals and between ethnic groups. Such differences in pathogenic mechanisms and susceptibility to glomerular injury are likely to require different therapeutic strategies. Second, the natural history of IgAN is most often slowly progressive; although >20% of affected patients progress to end-stage renal disease (ESRD), this may take 20 years or more.[57] Surrogate markers of disease progression are therefore often used as primary outcome measures rather than development of ESRD or mortality in order to make the study design practical. The validity of such markers, which include proteinuria reduction, reduction of episodes of visible hematuria, or doubling of serum creatinine, in predicting ESRD is variable. Third, a number of the older studies were performed when the generic approach to proteinuric nephropathies (accepted BP targets and use of renin–angiotensin blockade) was not so well established, making outcomes from these studies difficult to interpret for patients treated with current supportive treatment strategies. Fourth, many of the published trials recruited patients with preserved renal function. It is therefore unclear whether treatment, particularly with immunosuppressive agents, is appropriate when there is already significantly reduced renal function. It has been hypothesized that there may well be a 'point of no return' when significant tubulointerstitial fibrosis and glomerulosclerosis make the chance of treatment response very low, and outweighed by the toxicity of treatment.[58] Finally, all published studies have predominantly used clinical entry criteria, rather than histological grading, to determine selection for treatment. This is in complete contrast to drug trials in, for instance, lupus nephritis, where histological features have an important role in determining treatment choice. Preliminary results using the Oxford Classification of IgAN suggest that specific glomerular lesions may be more amenable to immunosuppression (mesangial or endocapillary proliferation), while extensive glomerulosclerosis and tubulointerstitial fibrosis suggest a lack of response to immunosuppression, and that the kidneys have reached the 'point of no return'.[45] Use of the Oxford Classification in directing immunosuppressive choices in IgAN requires testing in RCTs.

Risk stratification and who should we be treating

Patients with IgAN who have preserved renal function, microhematuria, and minimal proteinuria generally have a benign natural history.[59,60] Although this patient group does not require specific treatment, annual follow-up is advised to ensure early identification and treatment of *de novo* hypertension and increasing proteinuria.[61] Although it seems likely that proteinuria is a continuous risk factor, registry data suggest a threshold of 1 g/24 h, below which the negative impact on outcome is very modest. Registry data also demonstrate that reduction of proteinuria to <1 g/24 h results in significantly improved renal survival.[62] In such patients, there is consensus that renin–angiotensin blockade should be maximized and BP treated to agreed national targets before considering other forms of treatment.

Renin–angiotensin blockade

Renin–angiotensin blockade with an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) to control hypertension and reduce proteinuria to <0.5 g/24 h is beneficial in slowing the progression of proteinuric IgAN.[63–65] Although dual blockade using both an ACEi and an ARB reduces proteinuria in IgAN,[66] long-term beneficial effects on renal survival have not been demonstrated, and safety concerns remain regarding this approach.[67] The direct renin inhibitor, aliskiren, has recently been used in an open-label pilot study in addition to an ARB, resulting in additional reduction of mean protein excretion by 26.3% over a 12-month period, although 6 out of 25 patients experienced transient hyperkalemia.[68] Longer-term studies are needed with these approaches.

A significant proportion of patients will not achieve lowering of proteinuria to the target of <0.5–1 g/24 h despite maximal doses of an ACEi or ARB and are therefore at increased risk of progressive chronic kidney disease.[69] The choice of any additional therapy remains controversial.

Therapies often considered in addition to renin–angiotensin blockade and blood pressure control

Fish oils. The role of prescription-strength fish oil (the omega-3 fatty acids eicospentanoic and doxosohexanoic acid) remains uncertain. Proposed beneficial anti-inflammatory effects include reduction in eicosanoid and cytokine production, changes in membrane fluidity and rheology, and reduced platelet aggregability.[70] Fish oil is widely prescribed in IgAN, and its administration appears to be safe, although tolerability is a major issue because of a 'fishy' odor to the breath and perspiration, and gastrointestinal side effects including eructations and flatulence. One RCT has shown that treatment with fish oil provided long-term protection of renal function over 6 years of follow-up in patients with IgAN, with a creatinine clearance of 80 ml/min and protein excretion between 2.5 and 3 g/day.[71,72] However, in a separate RCT, where patients were allocated to receive omega-3 fatty acids, alternate day prednisolone, or placebo, no beneficial effect was observed in the fish oil group after 2 years of follow-up.[73] Other smaller RCTs also showed no benefit, and a meta-analysis suggested that the available evidence is inconclusive for the role of fish oil in IgAN, attributing much of the variability found in the separate studies to differences in the length of follow-up.[74] Further studies in this area are required before any firm conclusions can be drawn.

Tonsillectomy. Proponents of tonsillectomy believe the tonsils are a significant source of poorly galactosylated IgA1 *O*-glycoforms in IgAN. Tonsillectomy reduces the frequency of acute episodes of visible hematuria where tonsillitis is the provoking factor,[75] and there are those that also advocate tonsillectomy as a treatment to reduce progression to ESRD in IgAN. Observational studies have provided conflicting data regarding whether tonsillectomy improves long-term renal survival, with studies from Japan suggesting benefit,[76,77] while this is not supported by European studies.[78,79] In a recent non-randomized study of 55 patients with a mean baseline creatinine clearance of 95 ml/min and protein excretion of 1–1.5 g/day, comparing tonsillectomy and corticosteroid therapy vs. corticosteroid monotherapy, more patients in the tonsillectomy group had reduction of proteinuria and of episodes of visible hematuria at 24 months,[80] although the study was underpowered to draw conclusions about long-term outcomes. In subjects who had a follow-up biopsy at 24 months, the degree of IgA deposition and mesangial proliferation was reduced in those who had undergone tonsillectomy. A recently published meta-analysis of the efficacy of tonsillectomy in IgAN concluded that tonsillectomy alone did not improve the outcome; however, when combined with steroid therapy there did appear to be a renoprotective effect.[81] Given the significant morbidity of tonsillectomy, there remains a pressing need for an RCT to resolve the uncertainty about its role in IgAN.

Corticosteroids. The benefit of corticosteroid therapy over maximal supportive therapy with renin–angiotensin blockade remains controversial. The largest published RCT from Italy showed that treatment with corticosteroids reduced proteinuria and prevented progression to ESRD over a 10-year period.[82] However, the high-dose corticosteroid regimen used—'pulse' methylprednisolone (1 g daily for 3 days at induction and at the beginning of months 2 and 4) and alternate-day oral prednisolone (0.5 mg/kg) for 6 months—is felt by many clinicians to carry considerable toxicity, although none was reported in this study. Renin–angiotensin blockade was only used in a minority of patients in this study, although equally distributed between the treatment arms, and achieved BP was higher than current treatment goals. Two more recent trials have sought to address these issues, comparing treatment with corticosteroids plus renin–angiotensin blockade vs. renin–angiotensin blockade alone, in patients with preserved renal function (mean estimated glomerular filtration rate approximately 100 ml/min per 1.73 m^2) and proteinuria >1 g/24 h despite renin–angiotensin blockade.[83,84] In the Italian study, combination of an ACEi and a 6-month course of oral prednisolone appeared to be beneficial in terms of a reduction in the proportion of patients reaching the combined end point of doubling of serum creatinine or ESRD,[83] while in the Chinese study the proportion of patients who reached the primary end point of 50% increase in serum creatinine was reduced from 24 to 3% in the combination ACEi and corticosteroid therapy group.[84] Both studies have, however, been criticized as ACEi and ARB had to be stopped before both trials and there was no run-in period where renin–angiotensin blockade was maximized before commencement of immunosuppression, and therefore patients entering into these trials may have responded to ACEi/ARB treatment alone.[85] A recent meta-analysis of steroid therapy, which included these two studies, concluded that steroid therapy was associated with a decrease in proteinuria and with a statistically significant reduction of the risk in ESRD.[86]

Although based on anecdotal evidence, there does seem to be a clear benefit of corticosteroid therapy in the small number of patients with the abrupt onset of nephrotic syndrome in which IgA deposition is seen coinciding with minimal change morphology on light microscopy. These patients should be treated as for minimal change disease without IgA deposits, and respond in a similar fashion.[87]

Other immunosuppressive agents. Treatment of IgAN using corticosteroids in combination with other immunosuppressive agents remains a controversial area, where evidence is derived mainly from small trials, many performed in an era when the generic approach to glomerular disease was less well defined, such that BP targets and use of renin–angiotensin blockade were extremely variable.

Azathioprine. An RCT with a median follow-up period of 4.9 years showed no benefit of the addition of azathioprine to a 6-month high-dose corticosteroid regimen, either in maintaining renal function or in reducing proteinuria. Furthermore, azathioprine increased the risk for adverse effects, including hepatotoxicity, cytopenias, and gastrointestinal symptoms.[88]

Cyclophosphamide. A small single-center study of 38 patients with high-risk progressive IgAN, defined by an increase in serum creatinine by at least 15% during the year before study entry, showed that treatment with prednisolone and cyclophosphamide for 3 months, followed by azathioprine, produced a significant reduction in proteinuria, and improved renal survival over a 5-year follow-up period.[89] However, the control group was treated with no specific therapy, and BP control and renin–angiotensin blockade fell outside the current recommendations. Other RCTs involving the use of cyclophosphamide in IgAN have shown no consistent benefit.

Mycophenolate mofetil. The evidence for use of mycophenolate mofetil (MMF) is also unclear.[90,91] A meta-analysis reviewing the use of MMF in IgAN suggested no significant benefit regarding reduction of proteinuria.[92] However, the four studies included only recruited a total of 168 patients, follow-up was short, and a large number of patients already had evidence of advanced chronic kidney disease. The most recent report providing longer follow-up data on 40 Chinese patients with mild histological lesions did show benefit in reducing the composite end points of doubling of serum creatinine or ESRD.[93] Further trials are ongoing to assess the role of MMF in patients with persistent proteinuria despite maximal renin–angiotensin blockade; hopefully, these will clarify the role of MMF in the treatment of IgAN.

Other immunosuppressive agents. There are preliminary data from non-randomized studies of a number of other immunosuppressive and anti-inflammatory agents. Sirolimus has been shown to reduce proliferative glomerular lesions at 12 months, compared with the standard therapy using an ACEi and statin.[94] Wormwood (*Artemisia absinthium*), which reduces renal tumor necrosis factor-α levels, has been shown to reduce proteinuria significantly in patients with uncontrolled proteinuria despite dual renin–angiotensin system blockade.[95] The achieved reduction of proteinuria was sustained over 6 months of treatment, and persisted over a further 6 months after the supplement was withdrawn. Clearly, both agents need more formal study before any firm conclusions about their role in treating IgAN can be made.

Crescentic IgA nephropathy. Patients with IgAN, rapidly progressive loss of renal function, and crescentic GN on biopsy are often treated in the same way as those with other forms of crescentic GN, that is, using high-dose corticosteroids and cyclophosphamide and, when indicated, plasma exchange. Evidence for this approach in IgAN is derived mainly from case series, and there have been no RCTs.[96] Response to treatment is worse in crescentic IgAN than in other forms of crescentic GN, and renal survival is estimated to be only 50% at 1 year and 20% at 5 years. This may be the consequence of significant pre-existing chronic damage at the time of a crescentic transformation, thereby reducing the chances of a response to immunosuppression.

Recurrence following transplantation. Recurrence of IgA deposition following renal transplantation is very common, affecting between 30 and 50% of the patients over 5 years.[97] However, graft failure due to recurrence is relatively rare, and most often occurs in younger patients and in those who have had a rapidly progressive original course (e.g., crescentic IgAN or Henoch–Schönlein purpura).[98] There is little evidence that the choice of post-transplant immunosuppression protocols modifies the risk of recurrence,[99,100] although one retrospective analysis suggests a lower rate of recurrent disease in patients who received anti-thymocyte globulin at induction[101] and a recently published analysis of the Australia and New Zealand Dialysis and Transplant Registry suggests recurrent disease is more common in patients who undergo steroid withdrawal.[102] There is currently no evidence to support any specific therapy regimen for recurrence of IgAN following renal transplantation although a single-center retrospective analysis has suggested that ACEi/ARB treatment may reduce the rate of decline of allograft function in recurrent IgAN.[103]

New avenues for therapies in IgAN. With advances in our understanding of the pathogenesis of IgAN, it is hoped that new therapeutic options will become available. The critical role of IgA immune complex formation would suggest immunosuppression could be useful in IgAN; however, trial data remain difficult to interpret. We are likely to have a clearer understanding of the role of immunosuppression when the results of the large German multicenter RCT (STOP-IgAN) are known. In this study, patients with IgAN and persistent proteinuria >0.75 g/day after optimal supportive therapy for at least 6 months are randomized to additional immunosuppressive treatment (corticosteroids if estimated glomerular filtration rate $\geqslant 60$ ml/min per 1.73 m^2; corticosteroids plus cyclophosphamide/azathioprine if estimated glomerular filtration rate <60 ml/min per 1.73 m^2).[104]

Targeted immunosuppression to sites of mucosal B-cell induction may in the future provide an alternative to the traditional regimens used in current trials. A recently reported pilot study of a new enteric formulation of the locally acting glucocorticoid budesonide (Nefecon(R)), designed to release the active compound in the ileocecal region, demonstrated a significant reduction in urinary albumin excretion.[105] Whether this effect was due to the systemic effects of budesonide or direct effects on Peyers patches and mucosal B-cell induction is currently not known.

Modulation of B-cell TLR activation may also offer a new strategy for interfering with mucosal B-cell activation and IgA immune complex formation in IgAN. TLR agonists are being evaluated as vaccine adjuvants and as treatment for cancer, while antibodies to TLRs and inhibitors of TLR signaling pathways are showing increasing potential as treatments for a number of diseases ranging from

autoimmunity to ischemia–reperfusion injury.[106] Small-molecule inhibitors are being developed to block the nucleic acid-sensing TLRs, which are implicated in a number of autoimmune diseases, such as systemic lupus erythematosus, and are gaining increasing interest as pathogenic triggers in IgAN;[38] these may prove to be useful in the future in modulating mucosal B-cell activation and synthesis of poorly galactosylated IgA1. Recent data show that stimulation of TLR7 and TLR9 may directly antagonize the immunosuppressive action of corticosteroids and that dual TLR7 and 9 inhibitors could offer a way to lower steroid dosage and thus reduce side effects,[107] an effect that might be accentuated further if combined with a locally acting glucocorticoid such as budesonide (Nefecon(R)). We may not, however, need to wait for licensing of these new agents; the antimalarial hydroxychloroquine is a potent inhibitor of TLR9 and, to a lesser extent, TLR7 and TLR8.[108] Hydroxychloroquine also inhibits antigen processing and presentation via alkalinization of proteasomes[109] and may therefore represent an immediate candidate for future clinical trials in IgAN.

Treatment overview

The evidence base for treatment of IgAN is gradually increasing in both the number and quality of published trials. There is consensus that supportive treatment with renin–angiotensin blockade and tight BP control should be the initial treatment. But there remains a subset of patients who have persistent proteinuria despite such supportive therapy who are at high risk for progressive disease. Here, there is still no consensus whether corticosteroids or other immunosuppressive agents mitigate the risk of progression with acceptable toxicity. The renal protective effect of the supportive regimen means that evaluation of any additional intervention will require large numbers of patients and long-term RCTs to conclusively demonstrate benefit, until robust surrogate outcome markers are developed. As a recent Cochrane review noted, 'IgA nephropathy remains a disease in search of adequately powered RCTs to reliably inform clinical practice'.[110] Further advances in the understanding of the pathogenesis of IgAN will hopefully lead to more disease-directed forms of treatment rather than the empirical regimens currently in use.

CONCLUSIONS

Over the past 43 years, IgAN has become recognized as the commonest pattern of primary glomerulonephritis in all countries where renal biopsy is widely practiced and is now accepted as an important cause of ESRD at all ages. Our goals over the next decade must be to build on the significant advances that have been made in our understanding of the pathogenic pathways operating in IgAN in the hope that they will provide the stimulus for specific therapies to interrupt immune complex formation and mesangial IgA deposition. Although we await these advances, it is imperative that we conduct high-quality clinical trials to finally establish the utility of standard immunosuppressive regimes when supportive therapy aimed at BP control and blockade of the renin–angiotensin system is not sufficient.

DISCLOSURE

All the authors declared no competing interests.

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